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M. TOSHNER ET AL.

Mendelian randomisation and experimental medicine approaches to interleukin-6 as a drug target in pulmonary arterial hypertension

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Shareable abstract (@ERSpublications)
Tocilizumab did not block IL-6 signalling in pulmonary arterial hypertension. Multicentre mendelian randomisation studies additionally did not demonstrate evidence for IL-6R in pulmonary arterial hypertension. https://bit.ly/3xkDxS5

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Abstract

Background Inflammation and dysregulated immunity are important in the development of pulmonary arterial hypertension (PAH). Compelling preclinical data supports the therapeutic blockade of interleukin-6 (IL-6) signalling.

Methods We conducted a phase 2 open-label study of intravenous tocilizumab (8 mg·kg^{-1}) over 6 months in patients with group 1 PAH. Co-primary end-points were safety, defined by incidence and severity of adverse events, and change in pulmonary vascular resistance. Separately, a mendelian randomisation study was undertaken on 11 744 individuals with European ancestry including 2085 patients with idiopathic/heritable disease for the IL-6 receptor (*IL6R*) variant (rs7529229), known to associate with circulating IL-6R levels.

Results We recruited 29 patients (male/female 10/19; mean±SD age 54.9±11.4 years). Of these, 19 had heritable/idiopathic PAH and 10 had connective tissue disease-associated PAH. Six were withdrawn prior to drug administration; 23 patients received at least one dose of tocilizumab. Tocilizumab was discontinued in four patients owing to serious adverse events. There were no deaths. Despite evidence of target engagement in plasma IL-6 and C-reactive protein levels, both intention-to-treat and modified intention-to-treat analyses demonstrated no change in pulmonary vascular resistance. Inflammatory markers did not

predict treatment response. Mendelian randomisation did not support an effect of the lead *IL6R* variant on risk of PAH (OR 0.99, p=0.88).

Conclusion Adverse events were consistent with the known safety profile of tocilizumab. Tocilizumab did not show any consistent treatment effect.